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Feb 14, 2002

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TITLE: THERAPEUTIC USE OF THE SMR1 PROTEIN, THE SMR1 MATURATION PRODUCTS, SPECIFICALLY THE QHNPR PENTAPEPTIDE AS WELL AS ITS BIOLOGICALLY ACTIVE DERIVATIVES

PUBLICATION-DATE: February 14, 2002

INVENTOR-INFORMATION:

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US-CL-CURRENT: 435/7.1; 435/7.2

CLAIMS:

What is claimed is:

1. A therapeutic method for preventing or treating diseases caused by a mineral ion imbalance in a mammal, said method comprising administering to the mammal a composition comprising a pharmaceutically active amount of an SMR1 protein, or a maturation product of the SMR1 protein or of one of its biologically active derivatives.
2. The therapeutic method according to claim 1 wherein said mammal is a human.
3. The therapeutic method according to claim 1, wherein the therapeutic composition comprises a protein of formula XQHNPR, wherein X is a hydrogen atom, an amino acid V, or a polypeptide VR, VRG, VRGP, VRGPR or VRGPRR, or one of its biologically active derivatives.
4. The therapeutic method according to claim 3 wherein the pentapeptide XQHNPR or one of its biologically active derivative peptides comprises one or more amino acids in the D-form.
5. The therapeutic method according to claim 1 wherein the therapeutic composition is a liquid solution.
6. The therapeutic method according to claim 1 wherein the therapeutic composition is a gel.
7. The therapeutic method according to claim 1 wherein the therapeutic composition is a dry powder.
8. The therapeutic method according to claim 1 wherein the therapeutic composition is a controlled drug delivery device.
9. The therapeutic method according to claim 1 wherein the therapeutic composition is administered locally near a site to be treated.
10. The therapeutic method according to claim 1 wherein the therapeutic composition is administered orally route.

11. A method for screening ligand molecules that specifically bind to a target receptor for an XQHNPR pentapeptide, comprising the steps of: a) preparing a confluent target cell culture monolayer or preparing a target organ specimen or a tissue sample; b) adding a candidate molecule to be tested in competition with a half-saturating concentration of labeled pentapeptide; c) incubating the cell culture, organ specimen or tissue sample of step a) in the presence of the labeled candidate molecule for a time sufficient for specific binding to take place; and d) quantifying the label specifically bound to the target cell culture, organ specimen or tissue sample.

12. A method for determining an affinity of ligand molecules that specifically bind to a target receptor for a XQHNPR pentapeptide, comprising the steps of: a) preparing a confluent target cell culture monolayer or preparing a target organ specimen or a tissue sample; b) adding a candidate molecule to be tested that has been previously labeled with a radioactive or a nonradioactive label; c) incubating the cell culture, organ specimen or tissue sample of step a) in the presence of the labeled candidate molecule for a time sufficient for specific binding to take place; d) quantifying the label specifically bound to the target cell culture, organ specimen or tissue sample.

13. A method for screening candidate ligand molecules that possess an agonist or an antagonist biological activity on a target receptor of an XQHNPR pentapeptide, comprising the steps of: a) preparing a biological material comprising a confluent target cell culture monolayer, a target organ specimen or a tissue sample in cryosections or slices; b) incubating the cell culture, organ specimen or tissue sample of step a) in the presence of (i) 10^{-10} - 10^{-5} M of a candidate molecule and (ii) a submaximal concentration of QHNPR for a time sufficient for an adenylate cyclase activation to take place; and c) quantifying adenylate cyclase activity present in the biological material of step a), respectively in the presence or in the absence of the candidate ligand molecule and in the presence or in the absence of a submaximal concentration of QHNPR.

14. A biologically active derivative of the XQHNPR polypeptide which has been obtained according to the method of claim 13, provided that said biologically active derivative does not have the following structure: Y-HNP-Z, wherein Y denotes a glutamine (Q) or a pyroglutamic acid residue and Z represents an OH group or a basic amino acid, the basic amino acid being a Lysine (K) or an Arginine (R).

15. A method for determining the amount of XQHNPR or one of its biologically active derivatives to be administered to a patient suffering from a mineral ion imbalance, comprising the steps of: a) incubating a labeled XQHNPR peptide with a polyclonal or a monoclonal antibody directed against the same peptide; b) bringing into contact immune complexes formed with a biological sample from a patient to be tested suspected to contain an endogenous non-labeled XQHNPR peptide; c) detecting monoclonal or polyclonal antibody-bound labeled peptides that have not been displaced by the endogenous non-labelled XQHNPR peptide contained in the biological sample in order to determine a concentration of said endogenous peptide that is contained in the biological sample; d) comparing the concentration of the XQHNPR peptide formed at step c) with the concentration of the XQHNPR peptide normally found in a healthy individual; and e) calculating the amount of a therapeutic composition, comprising a pharmaceutically active amount of an SMR1 protein, or a maturation product of the SMR1 protein or of one of its biologically active derivatives, necessary in order to supply the defect of the XQHNPR peptide in body fluids and tissues.

16. The method according to claim 15 wherein said XQHNPR peptide is QHNPR.

17. A composition comprising a pharmaceutically effective amount of: an SMR1 protein; an SMR1 maturation product; or a biologically active derivative of the above; in combination with a pharmaceutically effective amount of a molecule involved in regulation of mineral ion balance in the body.

18. The composition according to claim 17 wherein said SMR1 maturation product is an XQHNPR peptide.

19. The composition according to claim 18, wherein said XQHNPR peptide is a QHNPR pentapeptide or a polymer thereof.

20. The therapeutic composition according to claim 17, wherein the molecule involved in the regulation of the mineral ion balance in the body is parathyroid hormone (PTH).

21. A composition according to claim 17, wherein the molecule involved in the

regulation of the mineral ion balance in the body is calcitonin (CT).

22. A therapeutic composition according to claim 17, wherein the molecule involved in the regulation of the mineral ion balance in the body is 1,25-dihydroxyvitamin D.

23. A method for producing an SMR1 protein maturation product which comprises the steps of: a) optionally amplifying a nucleic acid coding for a desired polypeptide using a pair of primers specific for an SMR1 genomic or cDNA sequence; b) inserting a nucleic acid coding for SMR1 protein inserted in an appropriate vector; c) inserting a nucleic acid coding for furin in a suitable vector, said vector being the vector of step b) or said vector being a vector different from the vector of step b); d) culturing, in an appropriate culture medium devoid of serum, a cell host previously transformed or transfected with the recombinant vector of step b) and c); e) harvesting the culture medium and the cell host; f) separating or purifying, from said culture medium or from a pellet of a resultant host cell lysate, the thus produced polypeptide of interest; g) characterizing the produced polypeptide of interest; and h) optionally assaying for specific recognition of said peptide by a polyclonal or a monoclonal antibody directed against a WQHNPR peptide.

24. The method according to claim 23, wherein said SMR1 protein maturation product is an XQHNPR peptide.

25. The method according to claim 23, wherein said amplifying step a) is carried out by SDA, TAS, 3SR NASBA, TMA, LCR, RCR, CPR, Q-beta replicase or PCR.

26. The method according to claim 23, wherein the harvesting step e) is carried out by lysing the cell host by sonication or by an osmotic shock.

27. The method according to claim 23 wherein the WQHNPR peptide is a QHNPR peptide.

28. A method for screening candidate ligand molecules that possess an agonist or an antagonist biological activity on a target receptor of an XQHNPR pentapeptide, comprising the steps of: a) culturing a eukaryotic cell capable of synthesizing collagen; b) incubating the eukaryotic cell of step a) in beta-glycerophosphate in the presence of 10^{-10} to 10^{-5} M of the candidate molecule and in the presence of a submaximal concentration of QHNPR peptide; c) quantifying production of a specific metabolite in the presence or in the absence of the candidate ligand molecule and in the presence or in the absence of a submaximal concentration of QHNPR.

29. The method according to claim 28, wherein said specific metabolite is calcium, alkaline phosphatase or DNA synthesis.

30. A method for screening a candidate ligand molecule that possesses an agonist or an antagonist biological activity on a target receptor of an XQHNPR pentapeptide, comprising the steps of: a) preparing a confluent target cell culture monolayer or preparing a target organ specimen or a tissue sample in cryosections or slices; b) incubating the cell culture, organ specimen or tissue sample of step a) in the presence of 10^{-10} to 10^{-5} M of the candidate molecule and in the presence of a submaximal concentration of QHNPR; c) quantifying production of a corresponding metabolite, respectively in the presence or in the absence of the candidate ligand molecule and in the presence or in the absence of a submaximal concentration of QHNPR.

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TITLE: THERAPEUTIC USE OF THE SMR1 PROTEIN, THE SMR1 MATURATION PRODUCTS, SPECIFICALLY THE QHNPR PENTAPEPTIDE AS WELL AS ITS BIOLOGICALLY ACTIVE DERIVATIVES

PUBLICATION-DATE: February 14, 2002

INVENTOR-INFORMATION:

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APPL-NO: 08/ 801405 [PALM]
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US-CL-PUBLISHED: 435/7.1; 435/7.2
US-CL-CURRENT: 435/7.1; 435/7.2

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

The present invention pertains to the use of a peptide molecule consisting in a maturation product of SMR1 (Submandibular rat protein 1) of structural formula QHNPR, as well as the biologically active derivatives of the said peptide, for preventing or treating diseases associated with a mineral ion imbalance in a human or an animal body. More particularly, the present invention relates to the therapeutic use of the above-cited molecules for preventing or treating an hydro-mineral imbalance in organs and tissues such as kidney, bone, dental enamel, dental ivory, gut matrix, pancreas or glandular gastric mucosa. This invention also deals with therapeutic compositions comprising a pharmaceutically active amount of the above-described therapeutic molecules as well as with therapeutic methods using the said therapeutic compositions. Finally, the present invention relates to processes for selecting ligand molecules that possess an agonist or an antagonist biological activity on the target receptor of the QHNPR pentapeptide as well as to the selected ligand molecules themselves.

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L3: Entry 1 of 2

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TITLE: THERAPEUTIC USE OF THE SMR 1 PROTEIN AND ACTIVE DERIVATIVES THEREOF

PUBLICATION-DATE: December 26, 2002

INVENTOR-INFORMATION:

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US-CL-CURRENT: 530/350

CLAIMS:

1. A therapeutic method for preventing or treating diseases caused by a metabolic imbalance, such as a mineral ion imbalance in a mammal, said method comprising administering to the mammal a composition comprising a pharmaceutically active amount of an SMR1 protein, or a maturation product of the SMR1 protein or of one of its biologically active derivatives
2. A therapeutic method for preventing or treating a disorder affecting the bone in a mammal, said method comprising administering to the mammal a composition comprising a pharmaceutically active amount of an SMR1 protein, or a maturation product of the SMR1 protein or of one of its biologically active derivatives.
3. A therapeutic method according to claim 2 for preventing or treating osteoporosis
4. The therapeutic method according to claim 1 or 2 wherein said mammal is a human.
5. The therapeutic method according to claim 1 or 2, wherein the therapeutic composition comprises a peptide of formula XQHNPR, wherein X is a hydrogen atom, an amino acid V, or a polypeptide VR, VRG, VRGP, VRGPR or VRGPRR, or one of its biologically active derivatives.
6. The therapeutic method according to claim 5 wherein the peptide XQHNPR or one of its biologically active derivative peptides comprises one or more amino acids in the D-form.
7. The therapeutic method according to claim 1 or 2 wherein the therapeutic composition is a liquid solution
8. The therapeutic method according to claim 1 or 2 wherein the therapeutic composition is a gel
9. The therapeutic method according to claim 1 or 2 wherein the therapeutic composition is a dry powder
10. The therapeutic method according to claim 1 or 2 wherein the therapeutic composition is a controlled drug delivery device
11. The therapeutic method according to claim 1 or 2 wherein the therapeutic composition is administered locally near a site to be treated

12. The therapeutic method according to claim 1 or 2 wherein the therepeutic composition is administered by the orally route
13. A method for screening iigand molecules that specifically bind to a target receptor an XQHNPR peptide, comprising the steps of a) preparing a confluent target cell culture monolayer or preparing a target organ specimen or a tissue sample, b) Adding a candidate molecule to be tested in competition with a half-saturation concentration of labeled peptide; c) incubating the cell cultiure, organ spefimen or tissue sample of step a) in the presence of the labeled candidate molecule for a time sufficient for specific binding to take place, and d) quantifying the label specifically bound to the target cell culture, organ specimen tissue sample
14. A method for determining an affinity of ligand molecules that specifically bind to a target receptor for a XQHNPR peptide, comprising the steps of a) preparing a confluent target cell culture monolayer or preparing a target organ specimen or a tissue sample; b) adding a candidate molecule to be tested that has been previously labeled with a radioactive or a nonradioactive label; c) incubating the cell culture, organ specimen or tissue sample of step a) in the presence of the labeled candidate molecule for a time sufficient for specific binding to take place; d) quantifying the label specifically bound to the target cell culture, organ specimen or tissue sample.
15. A method for screening candidate ligand molecules that possess an agonist or an antagonist biological activity on a target receptor of an XQHNPR peptide, comprising the steps of: a) preparing a biological material comprising a confluent target cell culture monolayer, a target organ specimen or a tissue sample in cryosections or slices; b) incubating the cell culture, organ specimen or tissue sample of step a) in the presence of (i) 10.sup.-10-10.sup.-5 M of a candidate molecule and (ii) a submaximal concentration of QHNPR for a time sufficient for an adenylate cyclase activation to take place; and c) quantifying adenylate cyclase activity present in the biological material of step a), respectively in the presence or in the absence of the candidate ligand molecule and in the presence or in the absence of a submaximal concentration of QHNPR.
16. A biologically active derivative of the XQHNPR polypeptide which has been obtained according to the method of claim 15, provided that said biologically active derivative does not have the following structure: Y-HNP-Z, wherein Y denotes a glutamine (Q), a pyroglutamic acid residue, or a sequence of two aminoacids arginine-glutamine (RQ) and Z represents an OH group or a basic amino acid, the basic amino acid being a Lysine (K) or an Arginine (R) or said biologically active derivative does not have the sequence QHNLR or RQHNLR.
17. A method for determining the amount of XQHNPR or one of its biologically active derivatives to be administered to a patient suffering from a metabolic imbalance, such as a mineral ion imbalance, comprising the steps of a) incubating a labeled XQHNPR peptide with a polyclonal or a monoclonal antibody directed against the same peptide; b) bringing into contact immune complexes formed with a biological sample from a patient to be tested suspected to contain an endogenous non-labeled XQHNPR peptide, c) detecting monoclonal or polyclonal antibody-bound labeled peptides that have not been displaced by the endogenous non-labelled XQHNPR peptide contained in the biological sample in order to determine a concentration of said endogenous peptide that is contained in the biological sample; d) comparing the concentration of the XQHNPR peptide formed at step c) with the concentration of the XQHNPR peptide normally found in a healthy individual; and e) calculating the amount of a therapeutic composition, comprising a pharmaceutically active amount of an SMR1 protein, or a maturation product of the SMR1 protein or of one of its biologically active derivatives, necessary in order to supply the defect of the XQHNPR peptide in body fluids and tissues
18. The method according to claim 17 wherein said XQHNPR peptide is QHNPR.
19. A composition comprising a pharmaceutically effective amount of: an SMR1 protein; an SMR1 maturation product; or a biologically active derivative of the above, in combination with a pharmaceutically effective amount of a molecule involved in regulation of metabolic balance, such as a mineral ion balance, in the body
20. The composition according to claim 19 wherein said SMR1 maturation product is an XQHNPR peptide
21. The composition according to claim 20, wherein said XQHNPR peptide is a QHNPR pentapeptide or a polymer thereof.

22. The therapeutic composition according to claim 19, wherein the molecule involved in the regulation of the mineral ion balance in the body is parathyroid hormone (PTH)
23. A composition according to claim 19, wherein the molecule involved in the regulation of the mineral ion balance in the body is calcitonin (CT)
24. A therapeutic composition according to claim 19, wherein the molecule involved in the regulation of the mineral ion balance in the body is 1,25-dihydroxyvitamin D.
25. A method for producing an SMR1 protein maturation product which comprises the steps of: a) optionally amplifying a nucleic acid coding for a desired polypeptide using a pair of primers specific for an SMR1 genomic or cDNA sequence; b) inserting a nucleic acid coding for SMR1 protein inserted in an appropriate vector; c) inserting a nucleic acid coding for fibrin in a suitable vector, said vector being the vector of step b) or said vector being a vector different from the vector of step b). d) culturing, in an appropriate culture medium devoid of serum, a cell host previously transformed or transfected with the recombinant vector of step b) and c), e) harvesting the culture medium and the cell host, f) separating or purifying, from said culture medium or from a pellet of a to resultant host cell lysate, the thus produced polypeptide of interest; g) characterizing the produced polypeptide of interest, and h) optionally assaying for specific recognition of said peptide by a polyclonal or a monoclonal antibody directed against a QHNPR peptide
26. The method according to claim 25, wherein said SMR1 protein maturation product is an XQHNPR peptide.
27. The method according to claim 25, wherein said amplifying step a) is carried out by SDA, TAS, 3SR NASBA, TMA, LCR, RCR, CPR, Q-beta replicase or PCR
28. The method according to claim 25, wherein the harvesting step e) is carried out by lysing the cell host by sonication or by an osmotic shock
29. The method according to claim 25 wherein the VQHNPR peptide is a QHNPR peptide.
30. A method for screening candidate ligand molecules that possess an agonist or an antagonist biological activity on a target receptor of an XQHNPR peptide, comprising the steps of: a) culturing a eukaryotic cell capable of synthesizing collagen; b) incubating the eukaryotic cell of step a) in beta-glycerophosphate in the presence of 10.sup.-10-10.sup.-5 M of the candidate molecule and in the presence of a submaximal concentration of QHNPR peptide, c) quantifying production of a specific metabolite in the presence or in the absence of the candidate ligand molecule and in the presence or in the absence of a submaximal concentration of QHNPR
31. The method according to claim 30, wherein said specific metabolite is calcium, alkaline phosphatase or DNA synthesis
32. A method for screening a candidate ligand molecule that possesses an agonist or an antagonist biological activity on a target receptor of an XQHNPR pentapeptide, comprising the steps of a) preparing a confluent target cell culture monolayer or preparing a target organ specimen or a tissue sample in cryosections or slices, b) incubating the cell culture, organ specimen or tissue sample of step a) in the presence of 10.sup.-10-10.sup.-5 M of the candidate molecule and in the presence of a submaximal concentration of QHNPR, d) quantifying production of a corresponding metabolite, respectively in the presence or in the absence of the candidate ligand molecule and in the presence or in the absence of a submaximal concentration of QHNPR.
33. The use of an SMR1 protein, or a maturation product of the SMR1 protein or of one of its biologically active derivatives for the preparation of a medicament for preventing or treating diseases caused by a metabolic imbalance, such as a mineral ion imbalance in a mammal.
34. The use of an SMR1 protein, or a maturation product of the SMR1 protein or of one of its biologically active derivatives for the preparation of a medicament for preventing or treating a disorder affecting the bone in a mammal.
35. The use according to claim 34 for preventing or treating osteoporosis.
36. The use according to claim 33 or 34 wherein said mammal is a human.

37. The use according to claim 33 or 34, wherein the medicament comprises a peptide of formula XQHNPR, wherein X is a hydrogen atom, an amino acid V, or a polypeptide VR, VRG, VRGP, VRGPR or VRGPRR, or one of its biologically active derivatives.
38. The use according to claim 37 wherein the peptide XQHNPR or one of its biologically active derivative peptides comprises one or more amino acids in the D-form.
39. The use according to claim 31 or 34 wherein the medicament is a liquid solution.
40. The use according to claim 33 or 34 wherein the medicament is a gel.
41. The use according to claim 33 or 34 wherein the medicament is a dry powder
42. The use according to claim 33 or 34 wherein the medicament is a controlled drug delivery device.
43. The use according to claim 33 or 34 wherein the medicament is administered locally near a site to be treated.
44. The use according to claim 33 or 34 wherein the medicament is administered by the orally route.
45. A tissular receptor complex for the SMRI-pentapeptide of sequence QHNPR.
46. A tissular receptor complex according to claim 45 with a pHi of 5.58/5.64.+-0.30, mainly present in the medulla of kidney, and pancreas and in lesser extent in the bone trabecular matrix
47. A tissular receptor complex according to claim 45 with a pHi of 6.62 .+-0.35 mainly present in the glandular gastric mucosa.
48. The use of the tissular receptor according to claims 45 to 47 for screening ligands having an affinity for said receptor.
49. The use of the tissular receptor according to claim 48 comprising the steps of contacting said tissular receptor with a potential ligand under conditions allowing the binding of said potential ligand by said tissular receptor, and detecting the complex formed thereby
50. The use of an SMR1 protein or a maturation product of the SMR1 protein or one of its biologically active derivatives for the preparation of a medicament active on renal tubular reabsorption through the complex described in claim 45